THE EFFECT OF VITAMIN D_3 SUPPLEMENTATION ON THE RISK OF THE ONSET OF TYPE 2 DIABETES: are we overestimating its possible extra skeletal benefits?

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Vitamin D deficiency has been associated with the presence of multiple chronic non-skeletal pathologies (including cardiovascular diseases, hypertension, non-alcoholic hepatic steatosis, some neoplasms and diabetes), suggesting the possibility that this vitamin can have numerous pleiotropic effects at the extra skeletal level, thanks to the ubiquitous distribution of its receptor [1-3].

Among these non-skeletal chronic pathologies which are potentially associated with reduced circulating levels of vitamin D, type-2 diabetes mellitus (T2DM) has represented one of the most important focuses of scientific research in the last decade [4].

Several epidemiological studies have shown that patients with T2DM have reduced circulating levels of vitamin D with respect to the non-diabetic population (comparable for age, gender and degree of obesity) and that low vitamin D levels are associated with a greater prevalence of micro- and macro-vascular chronic diabetic complications [4-6]. Experimental models have further demonstrated that reduced vitamin D levels are associated with increased insulin resistance and impaired insulin secretion on the part of the beta-cell, in addition to high levels of various procoagulant factors and inflammatory markers, and that most of these disorders improve after vitamin D_3 administration [2, 4, 7].

On the basis of this evidence, various prospective observational studies have successively shown the existence of a significant correlation between reduced circulating levels of vitamin D and increased risk of developing T2DM (especially in patients with reduced glucose tolerance) [8], thus confirming the biological plausibility of the involvement of vitamin D in the onset of T2DM. Nonetheless, until now available findings have been exclusively based on data that do not allow us to define a possible causal role of vitamin D in the development of diabetes. In particular, it is still not clear whether vitamin D_3 supplementation is able to reduce the risk of developing diabetes.

A recent randomized clinical trial, published by Pittas et al. in the August issue of the *New England Journal of Medicine* [9], aims to provide an answer to this question. In this broad RCT, called the "D2d trial," the authors assembled a sample of over 2,400 adults (45% females, 67% Caucasian, average age = 60 years, average BMI = 32 kg/m^2) with a high risk of developing diabetes (that is, individuals with at least two of the following disorders: fasting glycemia between 100 and 125 mg/dL, glycemia two hours after OGTT between 140 and 199 mg/dL, and glycated hemoglobin between 5.7 and 6.4%) but who were not selected based on their baseline vitamin D status. Indeed, their average circulating 25-hydroxyvitamin D levels were 28 ± 10 ng/mL; only 21.7% of the sample had 25-hydroxyvitamin D baseline values < 20 ng/mL. By means of a randomized, double-blind study, these subjects were later assigned either to an active treatment group with high doses of vitamin D_3 (cholecalciferol 4,000

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IU daily, n = 1,211) or to treatment with a placebo (n = 1,212). Subjects underwent a follow-up exam after 2.5 years on average. The principal outcome of the study was the appearance of new cases of T2DM. During the trial, circulating vitamin D levels more than doubled in those subjects treated with cholecalciferol (average baseline values increased from 27.7 ng/mL to 54.3 ng/mL by the end of the study), while levels remained nearly unchanged in the group treated with the placebo (with average baseline values going from 28.2 ng/mL to 28.8 ng/mL by the end of the trial). The authors of the study observed that the risk of developing T2DM during the follow-up was substantially comparable in the group treated with cholecalciferol with respect to the group given the placebo (9.4 and 10.7 events every 100 persons per year; hazard ratio 0.88, 95% CI 0.75-1.04; p = 0.12) (Fig. 1). Overall adherence of the participants to the treatment was quite high (~86%), while the incidence of adverse events (including hypercalcemia, eGFR reduction and nephrolithiasis) was low, and perfectly comparable between subjects treated with daily doses of cholecalciferol and those taking the placebo.

Statistical analysis conducted on the above-mentioned subgroups of subjects did not show the presence of any significant differences between the two treatment groups (Fig. 2). In particular, the results of the study did not vary when the population was divided by gender, race, geographic latitude, incidence of obesity or even by baseline circulating levels of 25-hydroxyvitamin D (< 20 ng/mL vs. ≥ 20 ng/mL) [9]. Nonetheless, a post-hoc analysis of the data of a smaller group of participants (n = 103, 4.3% of the total) with baseline circulating 25-hydroxyvitamin D levels < 12 ng/mL (< 30 nmol/L) revealed that the risk of developing T2DM was significantly lower in subjects treated with cholecalciferol with respect to those given the placebo (hazard ratio 0.38, 95% CI 0.18-0.80). By contrast, in participants (n = 2,319, 95.7% of the total) with baseline 25-hydroxyvitamin D levels ≥ 12 ng/mL, the risk of developing T2DM was comparable in the two treatment groups (hazard ratio 0.92, 95% CI 0.78-1.08) [9].

The results of this broad RCT show that vitamin D_3 supplementation in high doses (4,000 IU/day of cholecalciferol per os) in pre-diabetic subjects (that is, with a high risk of developing diabetes) who were not selected for baseline vitamin D deficiency is well tolerated (with no toxicity risk for excessive cholecalciferol intake); yet such supplementation cannot be associated with any significant reduction in the onset of T2DM during the 2.5-year follow-up exam [9].

For the most part, these results confirm what had already been observed in a previous RCT with a smaller sample, which was published in 2016 [9]. In this Norwegian study, called the "Tromso Vitamin D and T2DM trial", 511 subjects with prediabetes (61% male, average age = 62 years, average BMI = 30 kg/m^2, and average 25-hydroxyvitamin D values = 24 ± 8 ng/mL) were randomized and treated with either a placebo or 20,000 IU cholecalciferol per week (roughly 2,900 IU/day) for a period of 5 years [9]. Similarly to what was observed in the "D2d trial", the authors of this study did not find any significant benefit of vitamin D_3 supplementation with respect to the onset of T2DM during the study's follow-up exam (hazard ratio 0.90; 95% CI 0.69-1.18) [9].

Based on the results of these two RCTs, we can conclude that vitamin D_3 supplementation in high doses (with daily doses of cholecalciferol varying between 2,900 and 4,000 IU) in adults with a high risk of diabetes who are not selected on the basis of circulating levels of 25-hydroxyvitamin D do not seem to have a significant protective effect on the risk of developing T2DM. In both clinical trials, such supplementation is only associated with an average reduction of 10-12% of the risk for developing T2DM during a follow-up period of between 2 and 5 years [9, 10].

This conclusion, of course, does not exclude the possibility that future randomized clinical trials with larger samples may be able to obtain statistically significant findings showing long-term benefits of treatment with cholecalciferol with regard to T2DM development

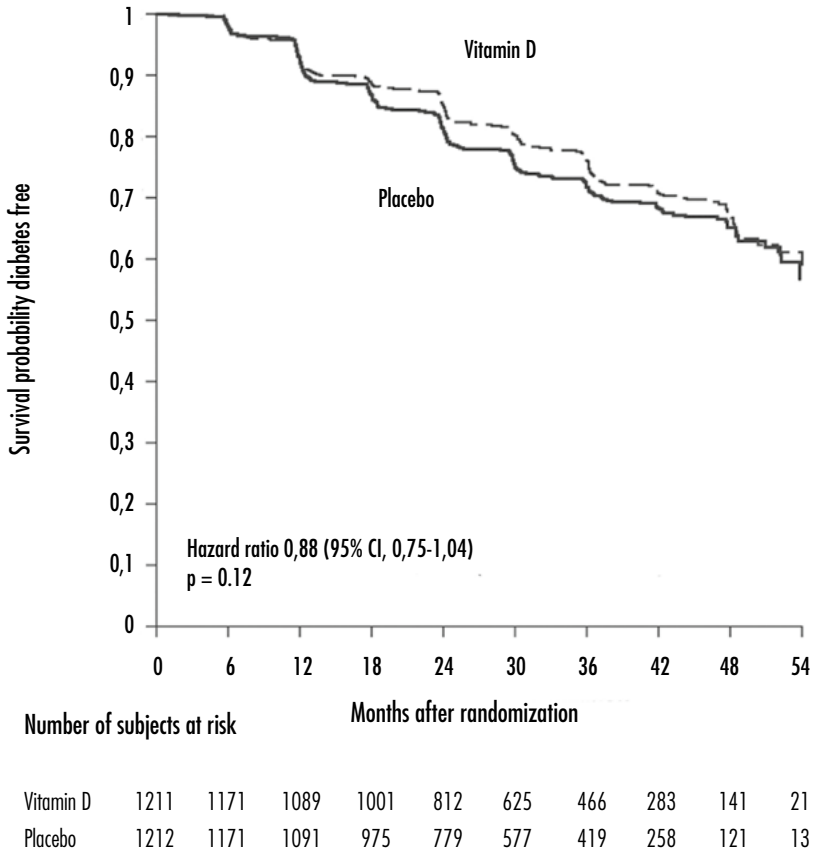

FIGURA 1.
Kaplan-Meier curve on effect of treating subjects with high doses of cholecalciferol (4,000 IU/day) vs. placebo on risk of developing T2DM in 2,423 prediabetic adult subjects. Data published in and taken from "D2d trial" [9].

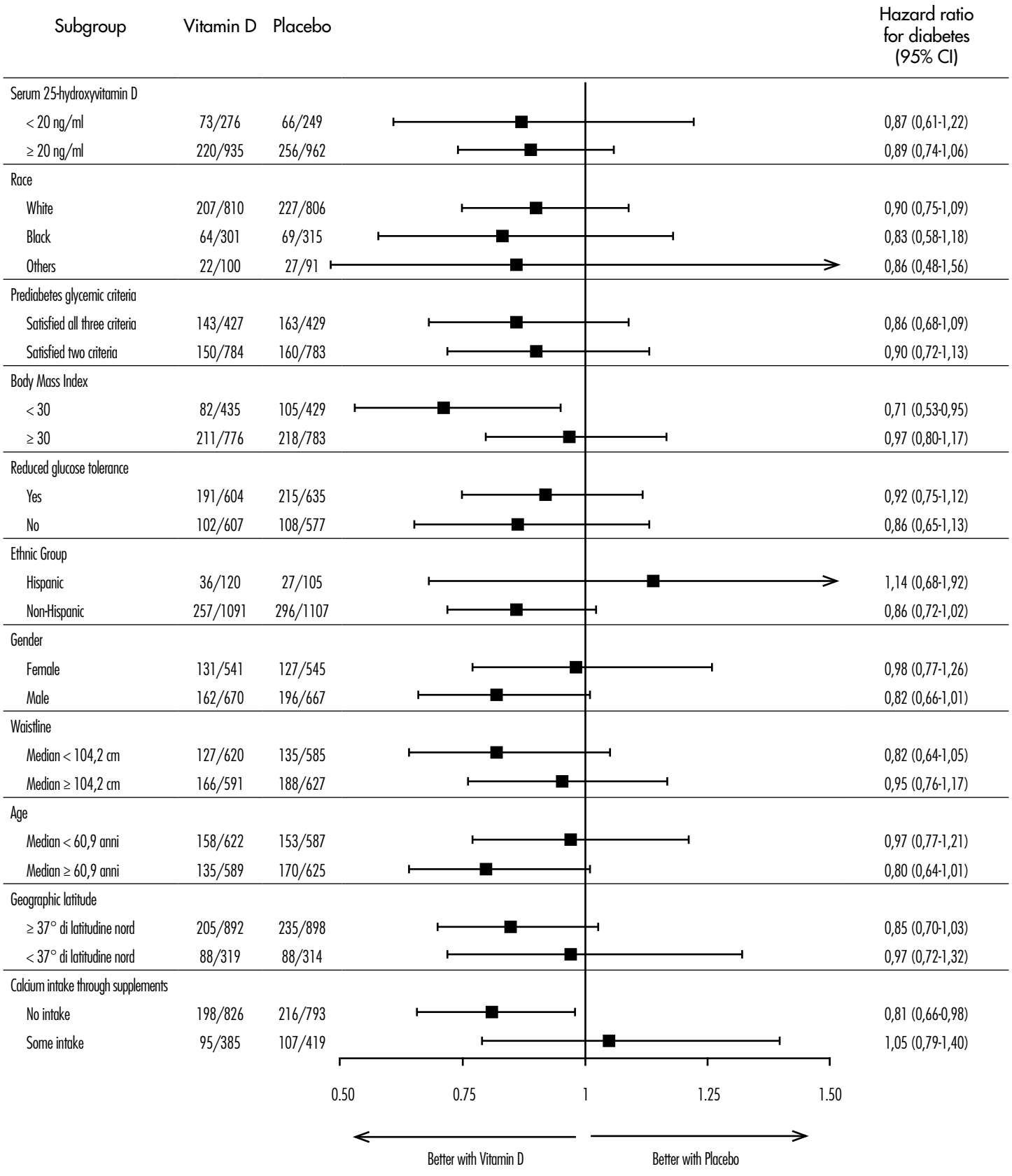

FIGURA 2.
Effect of treatment with high doses of cholecalciferol (4,000 IU/day) vs. placebo on risk of developing T2DM in various subgroups of specified prediabetic subjects. Data published in and taken from "D2d trial" [9].

(given that neither of the two clinical trials in question had a sample large enough to show a significant reduction in diabetes risk of 10-12%). Another factor that is even more important to emphasize is that the majority of subjects included in the two RCTs had optimal levels of circulating vitamin D levels [9, 10]. Indeed, in the "D2d trial", 42.2% of the participants had 25-hydroxyvitamin D levels ≥ 30 ng/mL, 36.1% had values between 20 and 29 ng/mL, while only 21.7% of the participants had 25-hydroxyvitamin D levels < 20 ng/mL [9]. It is, then, possible to hypothesize that the high percentage of subjects with adequate vitamin D levels who were included in these two RCTs may have reduced the researchers' ability to find benefits of cholecalciferol supplementation with regard to the risk of T2DM onset in the two treated groups.

It is furthermore useful to recall, as we have already seen, that a post-hoc analysis of data from the "D2d trial", conducted on participants (n = 103, 4.3% of the total) who had extremely low baseline circulating levels of 25-hydroxyvitamin D (< 12 ng/mL), itself suggested that the risk of developing T2DM was reduced by over 60% in subjects treated with cholecalciferol compared to those given the placebo (hazard ratio 0.38, 95% CI 0.18-0.80) [9]. In an increasingly evident manner, this fact underlines the need for researchers who plan future RCTs that evaluate the possible benefits of oral supplementation of vitamin D_3 on the risk of T2DM onset (and quite probably other important skeletal and extra skeletal outcomes as well, as has been shown in recent trials and meta-trials) [11-13] to take into account the vitamin D status of the participants enlisted in such trials. Such a measure seems justifiable given that it is reasonable to believe that the benefits of vitamin D_3 supplementation at high doses with regard to the long-term risk of developing T2DM may be greater in patients with vitamin D deficiency, compared to those who have adequate levels of circulating vitamin D [14].

CONFLICT OF INTEREST

The Author declares that he has no conflict of interest.

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